REVIEW ARTICLE

CONTINUUM AUDIO INTERVIEW AVAILABLE ONLINE

Emergent Management of Hypoxic-Ischemic Brain Injury

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ABSTRACT

OBJECTIVE: **This article outlines interventions used to improve outcomes for patients with hypoxic-ischemic brain injury after cardiac arrest.**

LATEST DEVELOPMENTS: **Emergent management of patients after cardiac arrest requires prevention and treatment of primary and secondary brain injury. Primary brain injury is minimized by excellent initial resuscitative efforts. Secondary brain injury prevention requires the detection and correction of many pathophysiologic processes that may develop in the hours to days after the initial arrest. Key physiologic parameters important to secondary brain injury prevention include optimization of mean arterial pressure, cerebral perfusion, oxygenation and ventilation, intracranial pressure, temperature, and cortical hyperexcitability. This article outlines recent data regarding the treatment and prevention of secondary brain injury. Different patients likely benefit from different treatment strategies, so an individualized approach to treatment and prevention of secondary brain injury is advisable. Clinicians must use multimodal sources of data to prognosticate outcomes after cardiac arrest while recognizing that all prognostic tools have shortcomings.**

ESSENTIAL POINTS: **Neurologists should be involved in the postarrest care of patients with hypoxic-ischemic brain injury to improve their outcomes. Postarrest care requires nuanced and patient-centered approaches to the prevention and treatment of primary and secondary brain injury and neuroprognostication.**

CITE AS:
CONTINUUM (MINNEAP MINN) 2024;30(3, NEUROCRITICAL CARE): 588–610.

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RELATIONSHIP DISCLOSURE:
The institution of Dr Steinberg has received research support from the University of Pittsburgh Clinical and Translational Science Institute.

UNLABELED USE OF PRODUCTS/INVESTIGATIONAL USE DISCLOSURE:
Dr Steinberg reports no disclosure.

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INTRODUCTION

Most patients who are resuscitated from cardiac arrest are unresponsive and require life-sustaining therapies because of hypoxic-ischemic brain injury. Neurologists should be involved in the clinical management of patients with hypoxic-ischemic brain injury to help improve their outcomes. Emergent management requires prevention and treatment of primary and secondary brain injury. Strategies to minimize primary brain injury focus on shortening the time to chest compressions and return of spontaneous circulation, as well as delivery of high-quality cardiopulmonary resuscitation (CPR).[1]

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Postarrest care aims to prevent secondary brain injury by preventing rearrest and restoring the balance of brain oxygen delivery and use. Key physiologic parameters important to secondary brain injury prevention include optimization of mean arterial pressure (MAP), cerebral perfusion, oxygenation and ventilation, intracranial pressure (ICP), temperature, and cortical hyperexcitability (FIGURE 2-1[2]). Different patients likely benefit from different treatment strategies, so an individualized approach to treatment and prevention of secondary brain injury is advisable. Neuroprognostication can guide the intensity of care and withdrawal of life-sustaining therapies and thus greatly affects outcomes for patients with hypoxic-ischemic brain injury. Although there are guidelines to help clinicians predict outcomes after cardiac arrest that use a multimodal approach, neuroprognostication is complex and often relies on clinical expertise. Many patients with hypoxic-ischemic brain injury recover and have favorable long-term outcomes, the likelihood of which improves with thoughtful and nuanced postarrest care.

EPIDEMIOLOGY OF CARDIAC ARREST

Sudden cardiac arrest is a leading cause of death and disability worldwide.[3] Annually, more than 150,000 adult Americans are admitted to the hospital for out-of-hospital cardiac arrest (OHCA),[4] and approximately 150,000 adult Americans achieve return of spontaneous circulation after in-hospital cardiac arrest.[5] Return of spontaneous circulation for patients with OHCA varies across

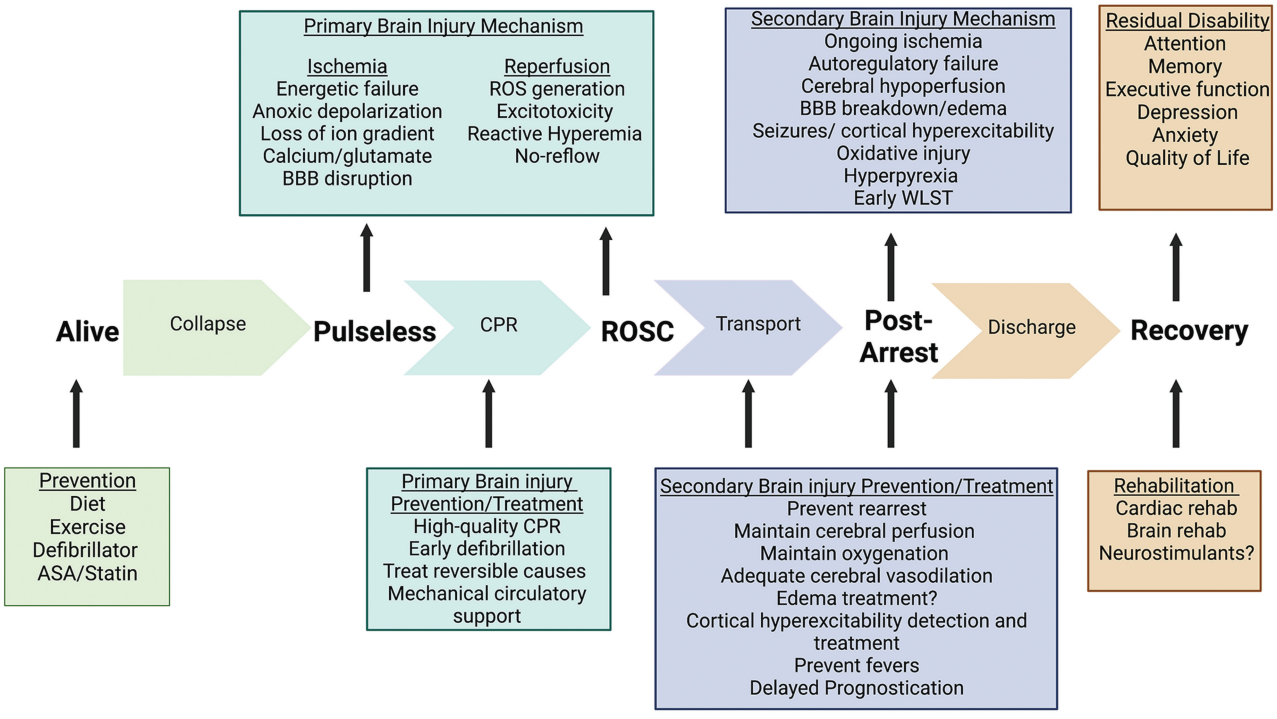

FIGURE 2-1

Preventing and treating secondary brain injury.

ASA = acetylsalicylic acid; BBB = blood-brain barrier; CPR = cardiopulmonary resuscitation; rehab = rehabilitation; ROS = reactive oxygen species; ROSC = return of spontaneous circulation; WLST = withdrawal of life-sustaining therapies.

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emergency medical service agencies, but survival to hospital admission is approximately 27%.[6] Return of spontaneous circulation is achieved in approximately 70% of patients with an in-hospital cardiac arrest.[7] The major underlying etiologies of both OHCA and in-hospital cardiac arrest are cardiac mechanisms (eg, acute coronary syndrome or arrhythmia from cardiomyopathy) and respiratory mechanisms (eg, exacerbation of chronic pulmonary disease or opioid overdose), which occur in 26% and 15% of patients, respectively.[8] Two percent of arrests are the result of a primary neurologic injury (eg, intracranial hemorrhage).[8] Each year, there are more than 23,000 pediatric out-of-hospital cardiac arrests in the United States,[9] most of which are caused by trauma, asphyxia, and sudden unexplained infant death.[10] More than 15,000 hospitalized children have an in-hospital cardiac arrest in the United States annually, with 80% to 90% achieving return of spontaneous circulation.[11] Most pediatric in-hospital cardiac arrests are caused by an underlying cardiac etiology.[11]

PATHOPHYSIOLOGY AND PREVENTION OF PRIMARY BRAIN INJURY

Understanding the mechanisms of primary and secondary brain injury is necessary to improve outcomes for patients with hypoxic-ischemic brain injury. Pathophysiology of hypoxic-ischemic brain injury can be conceptualized as a "two-hit" model, with primary brain injury caused by ischemia during pulselessness and reperfusion injury on return of spontaneous circulation, which is followed by secondary brain injury that may develop hours to days after initial resuscitation.[12]

During cardiac arrest, inadequate cerebral oxygenation causes neuronal ischemia and cell death within minutes.[13] Initially, the cessation of cerebral oxygen delivery impairs aerobic metabolism, causing a lack of ATP production, anoxic depolarization, and cytotoxic edema.[14] Anaerobic metabolism creates cerebral lactate accumulation, leading to intracellular acidosis,[15] which further raises intracellular calcium, causing mitochondrial toxicity.[16] The inability to maintain cellular respiration can lead to necrosis or trigger cascades that result in programmed cell death. After the return of spontaneous circulation, cerebral oxygen delivery is restored, but reperfusion injury can worsen brain damage.[17] Highly metabolically active structures are most susceptible to primary brain injury, including the hippocampi, thalami, cerebral cortex, corpus striatum, and cerebellar vermis.[18]

Strategies to minimize primary brain injury focus on shortening the time to chest compressions and return of spontaneous circulation.[1] Key actions are summarized by the American Heart Association's chain of survival and include immediate recognition of cardiac arrest with activation of emergency response systems, early CPR, and rapid defibrillation of shockable rhythms.[1] Laypeople can effectively deliver CPR without extensive training and apply automated external defibrillators.[19] Interventions to improve time to CPR and defibrillation include (1) protocols to enhance early recognition by laypeople and dispatchers, (2) dispatch-assisted CPR, (3) smart technologies for activation of lay responders, (4) increased public access to defibrillators, and (5) public education and training on CPR and defibrillation.[1] Many of these principles are paralleled in the management of in-hospital cardiac arrest and can be improved through the optimization of in-hospital systems of care.[20]

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PATHOPHYSIOLOGY AND PREVENTION OF SECONDARY BRAIN INJURY

After the return of spontaneous circulation, the injured brain is highly susceptible to new damage. Secondary brain injury is characterized by an imbalance between cerebral oxygen delivery and use.[12] Secondary brain injury can occur hours to days after the initial arrest and leads to worse outcomes. Hypoxic-ischemic brain injury can cause disruptions to cerebral autoregulation and oxygen delivery and can cause cerebral edema.[18] Fever and cortical hyperexcitability (ie, seizure) further worsen brain injury by increasing metabolic demand. Intensive care after cardiac arrest aims to prevent secondary brain injury by correcting these pathophysiologic processes and restoring balance to oxygen delivery and demand. Key targets for therapeutic interventions (FIGURE 2-1) are summarized in the following section.

Prevention of Rearrest

One in five people who experience cardiac arrest and transiently regain a pulse will rearrest within minutes, and rearrest is associated with worse survival.[21] Multiple parallel steps are needed to prevent rearrest and maintain the return of spontaneous circulation. Identifying treatable arrest etiologies is essential because some require immediate interventions (ie, thrombolytics for a massive pulmonary embolism or needle decompression for tension pneumothorax).[22] Clinicians must evaluate whether to initiate urgent treatments such as fluid resuscitation, vasoactive medications, inotropic support, and antiarrhythmic medications. After arrest, patients with ST elevations on ECG require immediate coronary angiography.[23-25] Timing of percutaneous coronary interventions for patients without ST elevations is controversial and requires an individualized approach (CASE 2-1).[26,27] Mechanical circulatory support (ie, extracorporeal membrane oxygenation, intraaortic balloon pump) may benefit unstable patients; the use of these interventions typically requires multidisciplinary discussion.

A neurologist may be asked for early risk stratification in this context. The degree of initial brain and systemic injury can be categorized by using risk stratification scores (ie, Pittsburgh Cardiac Arrest Category, revised post-Cardiac Arrest Syndrome for Therapeutic hypothermia [rCAST], and Full Outline of UnResponsiveness [FOUR]).[26,27] A neurologist's views on the patient's severity of injury may help clinical teams decide about performing aggressive interventions (ie, extracorporeal membrane oxygenation or cardiac catheterization). For patients with less severe initial injury, a neurologist may recommend pursuing more aggressive measures because these patients have a better chance of recovery (CASE 2-1). In contrast, interventions may not be done for a patient with a more severe initial injury because it has a lower likelihood of changing their outcome (CASE 2-2).

Autoregulation and Optimal Perfusion Pressure

Adequate cerebral perfusion is necessary to prevent secondary brain injury. Cerebral hypoperfusion may occur hours to days after arrest.[28] Normal cerebrovascular pressure autoregulation maintains constant perfusion through a range of arterial blood pressures, and neurovascular coupling matches local blood flow to metabolic demand (FIGURE 2-4[29]).[11] After hypoxic-ischemic brain injury, the lower limit of autoregulation (ie, the MAP below which oligemic flow occurs) is often right-shifted or sometimes absent.[30] The result is that cerebral perfusion

KEY POINTS

- Understanding the mechanisms of primary and secondary brain injury is important to improving outcomes in patients with hypoxic-ischemic brain injury.
- The pathophysiology of hypoxic-ischemic brain injury is conceptualized as a "two-hit" model with the initial primary brain injury followed by secondary brain injury that develops hours to days after initial resuscitation.
- Highly metabolically active structures are most susceptible to hypoxic-ischemic primary brain injury, including the hippocampi, thalami, cerebral cortex, corpus striatum, and cerebellar vermis.
- Strategies to minimize primary brain injury focus on shortening the time to chest compressions and return of spontaneous circulation in patients with cardiac arrest.

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may be inadequate, even in the absence of systemic hypotension, resulting in brain ischemia despite overtly normal MAP.[30,31] Multiple observational studies have demonstrated improved neurologic outcomes with a higher MAP (greater than 80 mm Hg).[32-34] Two small randomized trials compared a MAP of 65 to 75 mm Hg with 80 to 100 mg Hg and demonstrated a higher MAP was associated with lower levels of neurofilament light chain, a sensitive biomarker of neuronal brain injury, but did not affect the rate of favorable neurologic outcome.[31,35,36] A larger randomized controlled trial compared a MAP of 63 to 77 mg Hg and found no outcome difference (death or hospital discharge with poor neurologic examination within 90 days).[37] This study enrolled a

CASE 2-1

A 55-year-old woman was found with no pulse. Her husband performed cardiopulmonary resuscitation. Emergency medical services arrived, and she was defibrillated and had a return of spontaneous circulation after a total of 15 minutes of cardiopulmonary resuscitation.

Initial ECG showed non-ST-elevation myocardial infarction. On examination, she did not open her eyes to stimulation; had intact pupillary, corneal, and oculocephalic reflexes; demonstrated spontaneous respiratory rates above the minimum ventilator settings; did not have a cough or gag reflex; and extended her bilateral upper extremities to stimulation. Head CT showed no acute findings. The neurologist and interventional cardiologists discussed her case, and cardiac catheterization revealed 100% occlusion of her left anterior descending artery.

She was started on temperature control targeting 36°C (97°F). Her mean arterial pressure goal was greater than 65 mm Hg because she was in severe cardiogenic shock. Her EEG showed a continuous background with generalized periodic discharges at 2.5 Hz, consistent with the ictal-interictal continuum. Her EEG was reactive and variable (FIGURE 2-2). She was started on propofol, levetiracetam, and valproic acid.

Over the next 2 days, she remained in a coma but regained all brainstem reflexes. She flexed her bilateral upper extremities but developed stimulus-induced myoclonus. Her EEG continued to show generalized periodic discharges, but they had no correlation with the myoclonus. Clonazepam was added to her antiseizure regimen, which led to improvement on the EEG recording. Three days after arrest, somatosensory evoked potentials showed present N20 potentials bilaterally. Five days after arrest, she was still not awake. MRI showed some focal cortical diffusion restriction of occipital regions bilaterally. During a goals-of-care discussion with her husband, the neurologist explained that her prognosis was indeterminate and the extent to which she would improve would only be evident in the next 3 months. Her husband decided that she should undergo tracheostomy and percutaneous endoscopic gastrostomy tube. On hospital day 14, she regained consciousness but continued to have myoclonus. She was discharged to rehabilitation.

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population with a high incidence of layperson CPR and shockable rhythms, and nearly three-quarters of trial participants had functionally favorable survival. The trial may have been enriched with patients who had relatively mild brain injury and, thus, preserved cerebrovascular pressure autoregulation. Possibly, fewer patients who could benefit from higher MAP goals were enrolled in the trial because there were patients with less severe brain injury with impaired autoregulation. Whether the trial results apply to patients with more severe brain injury and effective strategies to individualize MAP targets are important areas for future research (see CASE 2-1 and CASE 2-3 for examples of individualized MAP goals).

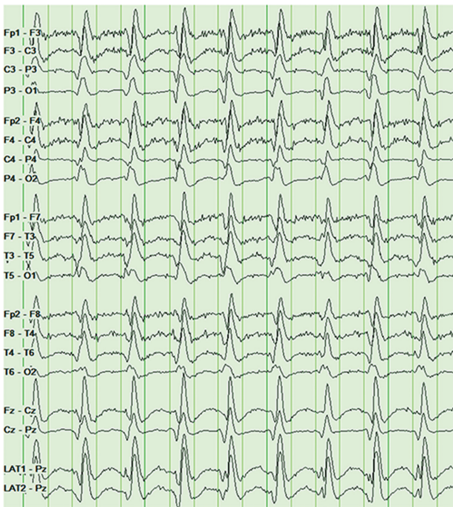

FIGURE 2-2
EEG from the patient in CASE 2-1 showing generalized periodic discharges that at times reach 2.5 Hz with a continuous background.

COMMENT

This patient's initial primary brain injury seemed mild based on early risk stratification, so cardiac catheterization was performed to prevent rearrest, and secondary brain injury was minimized through individualized targets including a mean arterial pressure goal greater than 65 mm Hg (because she was in cardiogenic shock). She was treated with targeted temperature management, and her ictal-interictal continuum was treated because the EEG showed a continuous background and reactivity. Because she remained comatose, prognostication was based on multimodal testing, and goals-of-care discussions emphasized her indeterminate prognosis and used shared decision making. She had delayed awakening and Lance-Adams syndrome, a postanoxic movement disorder consisting of multifocal myoclonus that is worse with action and psychological distress.

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Ventilator Management

Current recommendations are to maintain normoxia after cardiac arrest.[38] Hyperoxia may contribute to oxidative stress, and severe hypoxia is associated with worse outcomes after cardiac arrest.[39,40] The optimal Pa_{O_2} is unknown. A randomized controlled trial compared Pa_{O_2} target ranges of 68 to 75 mm Hg with 98 to 105 mm Hg and found no difference in the primary outcome of death and severe neurologic injury.[41] In most patients, targeting a Pa_{O_2} of 75 to 100 mm Hg is reasonable, and both hypoxia and severe hyperoxia should be avoided.[38] When oxygen monitoring is more difficult, such as in an out-of-hospital environment, more liberal oxygen use is preferred because conservative targets have been found to increase mortality in randomized trials.[42] Studies of direct brain tissue oxygen monitoring have found that some patients with recoverable

CASE 2-2

A 30-year-old man was found with no pulse and did not receive bystander cardiopulmonary resuscitation. When emergency medical services arrived, his initial rhythm was pulseless electrical activity. He received a total of 40 minutes of cardiopulmonary resuscitation. He arrived at the emergency department in shock with an initial lactate of 18 mg/dL. His urine drug screen was positive for opiates, so his arrest etiology was thought to be from an overdose. On initial examination, he did not open his eyes to stimulation, had absent brainstem reflexes, overbreathed the ventilator, and did not move any limbs to noxious stimulation, but he did have myoclonus. On head CT performed 2 hours after the return of spontaneous circulation, he had severe edema (FIGURE 2-3A).

He was admitted to the intensive care unit and started on targeted temperature management to 36°C (97°F) and pressors for a mean arterial pressure goal greater than 80 mm Hg. He had an intraparenchymal monitor placed for intracranial pressure (ICP) measurement and was placed on continuous EEG, which initially showed burst suppression, and was treated with a propofol drip and levetiracetam, which led to a cessation of myoclonus (FIGURE 2-3B).

After 24 hours, he was rewarmed. His ICP increased to 70 mm Hg (normal is less than 25 mm Hg), and he received a bolus of hypertonic saline. His EEG became isoelectric (FIGURE 2-3C). He remained comatose when sedation was discontinued, did not regain any brainstem reflexes, and no longer overbreathed the ventilator. A repeat CT of his head showed diffuse cerebral edema and effacement of sulci and cisterns (FIGURE 2-3D). Over the next few days, he underwent formal brain death testing and was declared dead by neurologic criteria.

COMMENT

This patient had a significant primary brain injury. An attempt was made to prevent and treat secondary brain injury (including elevating mean arterial pressure goals, temperature control, treatment of postanoxic myoclonus, and ICP management). However, given the severity of primary brain injury, these interventions did not improve the outcome, and he died.

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hypoxic-ischemic brain injury develop diffusion-limited oxygen delivery attributed to perivascular edema (ie, astroglial edema).[43] These patients may develop ischemic neuronal injury despite grossly normal MAP and PaO_2.[44] Strategies to titrate PaO_2 based on individual need are an important area of ongoing research.

Cerebral blood flow can be affected by ventilation.[25] Hyperventilation results in hypocapnia, leading to cerebral vasoconstriction, and can subsequently cause cerebral ischemia.[45] Mild therapeutic hypercapnia can improve cerebral blood flow and may reduce biomarkers of brain injury,[45] although early-phase trial data are mixed.[35] A 2023 randomized controlled trial showed no difference in favorable neurologic outcomes or survival for patients who received mild hypercapnia compared with normocapnia.[47] Higher carbon dioxide levels can

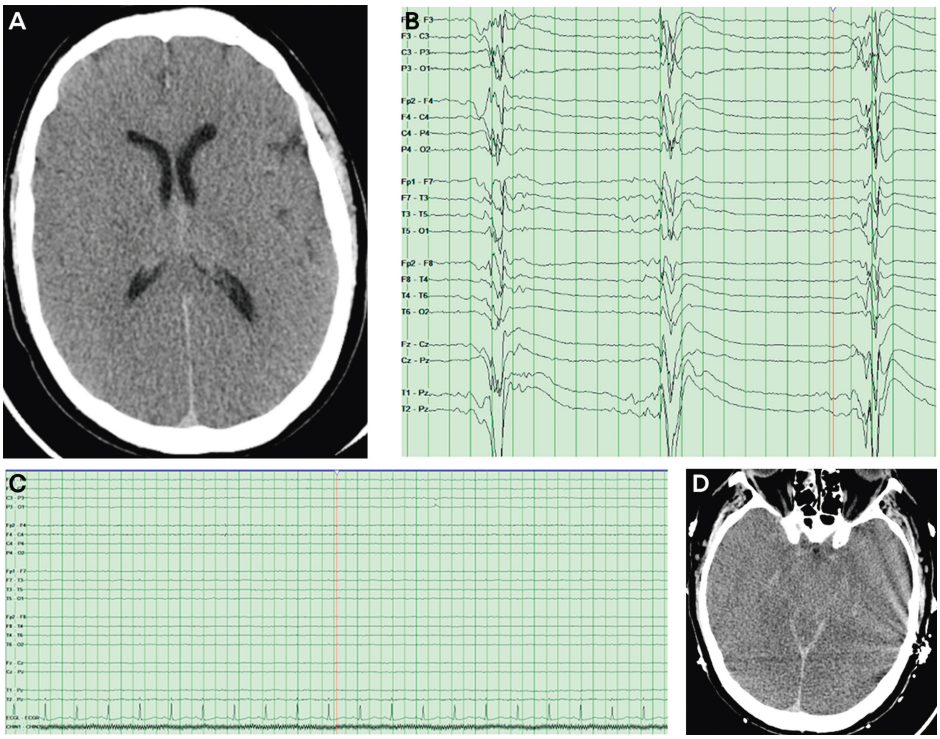

FIGURE 2-3

Findings from the patient in CASE 2-2. *A*, Initial axial noncontrast head CT showing severe cerebral edema. *B*, Initial EEG with a burst-suppression pattern (on a suppressed background). *C*, EEG 24 hours later with isoelectric suppression (ECG artifact seen in EEG leads). *D*, Axial head CT 24 hours later with diffuse cerebral edema, effacement of sulci and cisterns, and a pseudosubarachnoid pattern (diffuse subarachnoid hyperdensity seen in patients with severe cerebral edema, mimicking subarachnoid hemorrhage).

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result in cerebral vasodilation, leading to more cerebral blood volume and increased ICP, resulting in worsened ischemia.[48] With unclear benefits of mild hypercapnia, current European Resuscitation Council and European Society of Intensive Care Medicine guidelines recommend targeting normocapnia ($PaCO_2$ 35 to 45 mm Hg) and avoiding hypocapnia.[38] However, a patient-specific approach is likely most beneficial. Of note, if targeted temperature management is used, blood gas results must be temperature corrected.

Intracranial Pressure and Edema

Cerebral edema is a common complication of hypoxic-ischemic brain injury.[49] When severe, cerebral edema increases ICP, resulting in herniation and potentially leading to brain death. Early cerebral edema seen on CT of the brain usually predicts a worse outcome (CASE 2-2), but some patients can recover (CASE 2-1 and CASE 2-3). Even radiographically occult edema localized to astrocyte end-feet may contribute to modifiable secondary brain injury by impairing capillary blood flow and increasing capillary–tissue oxygen gradients.[43] Elevated ICP can be measured with invasive and noninvasive monitors, allowing for goal-directed treatment (TABLE 2-1). Controversy exists about whether measurement and treatment of ICP should be done for patients with hypoxic-ischemic brain injury.[50,51]

It is unclear whether treatment of early severe cerebral edema improves outcomes.[50,52] For more information on treatment strategies for cerebral edema and elevated ICP, refer to the article "Emergent Management of Intracerebral

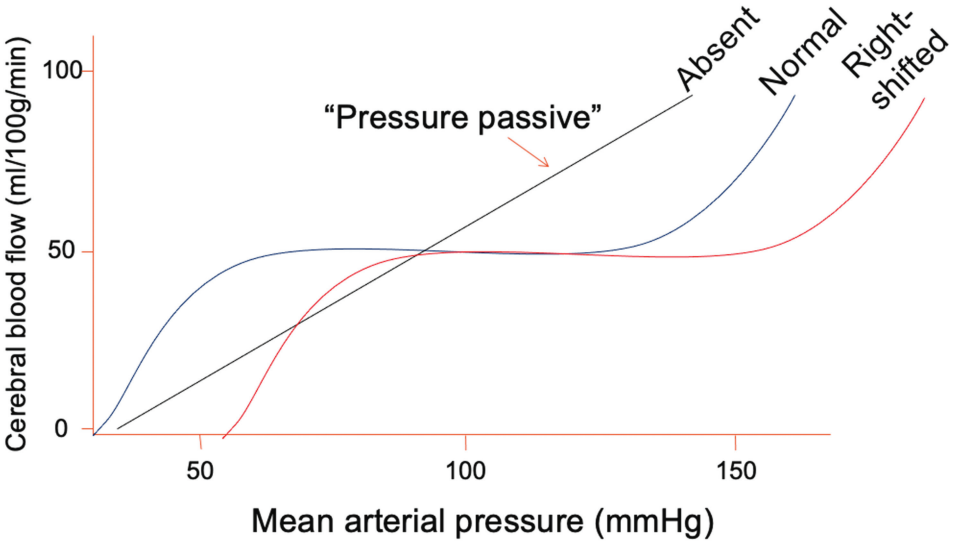

FIGURE 2-4

Autoregulation curve. Autoregulation is normally intact, so over a wide range of mean arterial pressures (MAPs) the cerebral blood flow is constant (*blue line*). After hypoxic-ischemic brain injury, the lower limit of autoregulation (ie, the MAP below which oligemic flow occurs) is often shifted to the right (*red line*) or sometimes absent (*black line*). The result is that cerebral perfusion or flow may be inadequate, even in the absence of systemic hypotension, resulting in brain ischemia despite normal MAP.

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Hemorrhage" by Santosh B. Murthy, MD, MPH, FNCS,[53] in this issue of *Continuum*. Early severe cerebral edema may be an epiphenomenon of severe primary hypoxic-ischemic brain injury, rather than a treatable cause of secondary brain injury. However, edema can also be caused or exacerbated by other insults that are modifiable and potentially preventable.[12] Rewarming after hypothermic temperature control may worsen cerebral edema,[54] so clinicians may consider taking a gradual approach to rewarming patients with mild to moderate cerebral edema. Cardiac arrest impairs the ability of the brain to buffer rapid shifts in serum osmolarity, so patients with hyperosmolar states (ie, hyperglycemia, uremia) at the time of arrest may develop cerebral edema with rapid correction of serum osmolarity (**CASE 2-3**). Invasive and noninvasive monitors may help allow for goal-directed care in these cases (**CASE 2-3** and **TABLE 2-1**).

Temperature Control

Hypothermic temperature control has historically been a major focus of reducing secondary brain injury after arrest for comatose patients. At the cellular level, hypothermia reduces cerebral metabolism, alters apoptotic cascades, improves glucose use, reduces seizure tendency, and lowers ICP.[12] Whether these preclinical effects translate into an outcome benefit for patients is uncertain, and the optimal target temperature is unknown. Small early trials demonstrated benefit from cooling to 32°C (90°F) to 34°C (93°F) compared with either normothermia or no temperature management.[55,56] Subsequently, much larger trials showed no outcome difference between 33°C (91°F) and 36° (97°F)[57] or between 33°C (91°F) and a strategy of fever avoidance.[58] These studies mostly enrolled patients with initial shockable rhythms who had layperson CPR. Another trial that enrolled patients with nonshockable rhythms found a benefit from cooling to 33°C (91°F) compared with normothermia.[59] In most of these trials, patients received hypothermic temperature control for 24 hours. **TABLE 2-2** summarizes targeted temperature management trials.[60,61]

It is unknown whether a longer or shorter duration of hypothermia is beneficial. Multiple observational studies suggest subsets of patients with hypoxic-ischemic brain injury may benefit from hypothermia, and individualized approaches to postarrest temperature management are an important area for future research.[60-64] Based on the data mentioned here, current European Resuscitation Council and European Society of Intensive Care Medicine recommendations are that, at a minimum, fever should be actively avoided after arrest[38] because each degree above 37°C (99°F) is associated with worse outcomes.[65] Hypothermia is also considered a reasonable treatment strategy.

Continuous core temperature monitoring is mandatory after arrest to prevent fever. Many patients require pharmacologic interventions and active temperature control measures to prevent fever.[58] When using targeted temperature management, there must also be close serial assessment for signs of discomfort or thermogenesis (ie, shivering). Shivering can result in an inability to meet temperature goals, so sedation with or without neuromuscular blockade is often required. If sedation is needed, short-acting medications, such as fentanyl, propofol, or dexmedetomidine, are preferred. Benzodiazepines may delay awakening and should generally be avoided.[66]

KEY POINTS

- Secondary brain injury reflects an imbalance between cerebral oxygen delivery and use in patients with hypoxic-ischemic brain injury.
- Intensive care after cardiac arrest aims to prevent secondary brain injury by correcting pathophysiologic processes, including the optimization of mean arterial pressure, cerebral perfusion, oxygenation and ventilation, intracranial pressure, temperature, and cortical hyperexcitability, to restore balance to oxygen delivery and demand.
- Adequate cerebral perfusion is necessary to prevent secondary brain injury and may require high mean arterial pressure goals because of impaired autoregulation in patients with hypoxic-ischemic brain injury.
- It is unclear whether patients with more severe hypoxic-ischemic brain injury benefit from a higher mean arterial pressure or whether individualized strategies are more effective.
- The optimal Pao_2 and $Paco_2$ after cardiac arrest is unknown, but European Resuscitation Council and European Society of Intensive Care Medicine guidelines recommend normoxia (Pao_2 75 to 100 mm Hg) and normocapnia ($Paco_2$ 35 to 45 mm Hg).
- Early cerebral edema usually predicts a worse outcome in patients with hypoxic-ischemic brain injury.

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Seizures

Many patients who are comatose after arrest develop hyperexcitable EEG changes.[67,68] Seizures may contribute to secondary brain injury, but it is unclear whether aggressive suppression of rhythmic or periodic EEG patterns improves neurologic outcomes.[69] A small randomized controlled trial demonstrated that neurologic outcomes of comatose patients were similar when rhythmic or periodic discharges (greater than 0.5 Hz) on EEG were treated with an aggressive antiseizure regimen compared with standard management.[70] Few patients had true electrographic seizures (10%) or a continuous background (18%).

Although the European Resuscitation Council and European Society of Intensive Care Medicine guidelines recommend treatment of generalized tonic-clonic seizures after arrest, these events are uncommon accompaniments of hypoxic-ischemic brain injury.[71] Antiseizure medications should be considered to treat myoclonus, nonconvulsive status epilepticus, or ictal-interictal continuum when a continuous or reactive background is observed (see the Neuroprognostication section and CASE 2-1).[68,72,73] After arrest, a transfer to a center with continuous EEG monitoring capability should be considered to

CASE 2-3

A 50-year-old man with a history of type 1 diabetes was brought to the emergency department with a decreased level of consciousness after feeling unwell for a few days. On arrival, he had a cardiac arrest, and a return of spontaneous circulation was achieved after 20 minutes. He had a blood glucose of 600 mg/dL (normal blood glucose level is 70 to 180 mg/dL) and was in diabetic ketoacidosis. He had an acute kidney injury with a creatinine level of 5 mg/dL (normal creatinine level is 0.7 to 1.3 mg/dL) and blood urea nitrogen of 90 mg/dL (normal blood urea nitrogen is 7 to 20 mg/dL). His serum osmolality was 320 mOsm/kg (normal serum osmolality is 275 to 295 mOsm/kg). He was comatose with intact brainstem reflexes and no motor response to noxious stimulation. His initial head CT showed moderate edema (FIGURE 2-5A). His continuous EEG was reactive and variable with a continuous background and no malignant features (FIGURE 2-5B).

He was started on a targeted temperature of 36°C (97°F), and a mean arterial pressure goal greater than 80 mm Hg was established. He was oliguric, hyperkalemic, and acidotic, so he needed continuous renal replacement therapy. Given the cerebral edema revealed on the head CT, elevated serum osmolarity, and uremia, an intraparenchymal monitor was placed to guide a slow correction of his serum osmolarity. On rewarming, his intracranial pressure (ICP) increased to 40 mm Hg (normal ICP is less than 25 mm Hg), and his brain tissue oxygen dropped to 10 mL O_2/100 g brain tissue (normal brain tissue oxygen level is greater than 20 mL O_2/100 g brain tissue). His continuous renal replacement therapy parameters and insulin drip rate were changed to ensure slower correction of serum osmolality. Eventually, his metabolic derangement improved. On day 4 after arrest, he regained consciousness. He was extubated and eventually discharged to rehabilitation.

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evaluate for seizures and for prognostication purposes. EEG background continuity can change over time[74] and intermittent EEG is insensitive to detecting epileptiform discharges.[75]

Myoclonus is common after cardiac arrest and was historically thought to indicate a universally poor prognosis. Modern data show that postanoxic myoclonus does not invariably predict poor outcomes.[72,76] EEG can help differentiate myoclonus subtypes associated with poor outcomes from those that can be seen in patients who are more likely to recover.[73,77] Development of a continuous cortical background on EEG despite postanoxic myoclonus is associated with delayed awakening (days to weeks). It is uncertain whether this reflects the underlying pathobiology of brain injury or sedation from antiseizure medicines that aim to suppress myoclonus. On recovery, these patients often develop Lance-Adams syndrome (CASE 2-1).

HETEROGENEITY OF TREATMENT RESPONSE

A patient-centered strategy for the treatment and prevention of secondary brain injury is necessary for patients with hypoxic-ischemic brain injury. Neutral findings from clinical trials that test a one-size-fits-all approach should not be

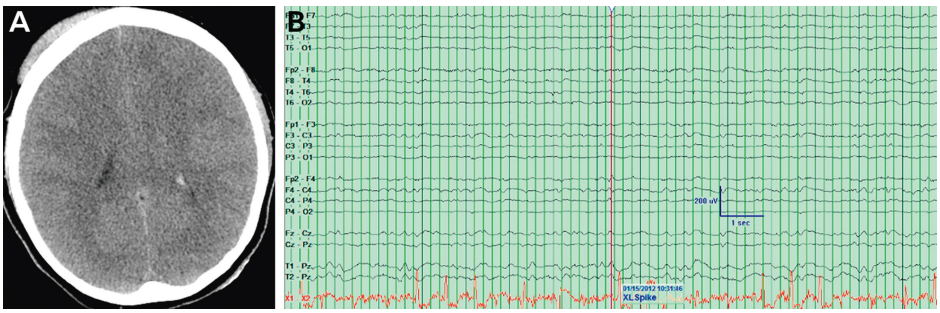

FIGURE 2-5
Findings from the patient in CASE 2-3. *A*, Axial head CT with diffuse sulcal effacement reflecting moderate cerebral edema. *B*, EEG showing a continuous, reactive, and variable background.

COMMENT

This case illustrates a patient with a low-risk stratification of severe brain injury with minimal primary brain injury based on examination, initial neuroimaging, EEG, and hemodynamics. Because the initial CT of his head showed moderate edema, an intraparenchymal monitor was placed to allow for tight control of the rate of decrease of serum osmolarity to avoid worsening the cerebral edema. When his ICP became elevated during rewarming, systemic physiologic parameters were adjusted to prevent worsening via secondary brain injury. Despite cerebral edema on his head CT, a tailored approach to secondary brain injury led to a good outcome.

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interpreted to mean that the trial intervention is inert.[64,78] It is biologically plausible that different patients benefit from different treatment strategies, a phenomenon that may be difficult to detect at a population level without testing an individualized approach to patient care. For example, a patient with minimal brain injury and severe cardiac dysfunction should likely be treated differently from a patient with severe brain injury and no cardiac dysfunction.[79] Neurologists should tailor postcardiac arrest care for patients based on their individual clinical characteristics. The best strategy to individualize patient care after cardiac arrest is an area of ongoing research and includes using machine-learning techniques.[64,79] See all three cases in this article for a comparison of approaches to secondary brain injury.

Experimental interventions and medications have been studied in patients after arrest, mostly in preclinical phases.[80,81] These potential neuroprotective agents are aimed at lessening excitotoxicity, improving neuronal metabolism, and decreasing mitochondrial injury and neuroinflammation.

NEUROPROGNOSTICATION

Accurate neuroprognostication for patients with hypoxic-ischemic brain injury affects patient outcomes.[82] For more information on this topic, refer to the article "Prognostication in Neurocritical Care" by Susanne Muehlschlegel, MD, MPH, FNCS, FCCM, FAAN,[83] in this issue of *Continuum*. Neuroprognostication after hypoxic-ischemic brain injury is complex and difficult.[84] Because of the inherent challenges of prognostication, clinicians often perform poorly and have variable, systemically biased, and error-prone expectations.[85,86] In a single-center study, clinicians incorrectly predicted both survival to hospital discharge and awakening from coma in one-third of cardiac arrest cases and reported high confidence in their false predictions.[85] Erroneously predicting there is no

TABLE 2-1 **Monitors Used for Secondary Brain Injury**

Parameter	Invasive monitoring	Noninvasive monitoring
Global neurologic function	None	Neurologic examination (Full Outline of UnResponsiveness Score [FOUR] score, Pittsburgh Cardiac Arrest Category [PCAC] score)
Autoregulation and perfusion pressure	Intraparenchymal monitor	Near-infrared spectroscopy, transcranial Doppler
Brain tissue oxygen	Partial pressure of oxygen in brain tissue ($PbtO_2$) probe	Near-infrared spectroscopy, jugular bulb catheter
Cerebral edema	None	CT, MRI
Intracranial pressure	Intraparenchymal monitor	CT, transcranial Doppler
Cortical hyperexcitability, seizure	Depth electrode	EEG, amplitude-integrated EEG, bispectral index
Metabolic crisis and failure	Microdialysis catheter	Jugular bulb catheter

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chance of awakening from coma leads to withdrawal of life-sustaining therapies for patients who might otherwise recover, resulting in thousands of avoidable deaths annually.[87] Incorrectly predicting the potential for awakening contributes to prolonged and costly care for some patients and can lead to survival with a quality of life incompatible with the patient's previously expressed wishes.

There is no gold standard approach to prognostication in hypoxic-ischemic brain injury, and the best diagnostic approaches leave many patients with an uncertain prognosis.[88,89] Guidelines developed by multiple societies (ie, European Resuscitation Council and European Society of Intensive Care Medicine, American Heart Association, and Neurocritical Care Society) exist to help clinicians prognosticate,[24,38,90,91] yet many clinicians do not follow them.[92] Guidelines outline the use of multimodal testing (TABLE 2-3[93] lists tests, and FIGURE 2-6 shows European Resuscitation Council guidelines). Test interpretation

Summary of Major Targeted Temperature Management Trials TABLE 2-2

Trial, year	Sample size	Inclusion criteria	Treatment arms	Outcome
Bernard et al, 2002[55]	77	Out-of-hospital cardiac arrest (OHCA), ventricular fibrillation, persistent coma	33°C (91°F) for 12 hours versus 37°C (99°F) (passive rewarming if cold)	Improved functional neurologic outcome in 33°C (91°F) arm
Hypothermia after Cardiac Arrest Study Group, 2002[56]	275	Witnessed OHCA, ventricular fibrillation or ventricular tachycardia, 5-15 minutes to emergency medical services, persistent coma	32-34°C (90-93°F) for 24 hours versus no temperature control	Improved functional neurologic outcome in targeted temperature management arm
Nielsen et al, 2013[57]	939	Glasgow Coma Scale score < 8 after OHCA due to "presumed cardiac" etiology, regardless of rhythm (excluded unwitnessed asystole)	33°C (91°F) versus 36°C (97°F) for 24 hours	No difference in survival or functional outcome
TTH48, 2017[60]	355	OHCA due to "presumed cardiac" etiology, regardless of rhythm (excluded unwitnessed asystole)	33°C (91°F) for 24 hours versus 33°C (91°F) for 48 hours	No difference in neurologic outcome or survival
Lascarrou JB, et al, 2019[59]	581	Nonshockable rhythms only	33°C (91°F) for 24 hours versus 37°C (99°F)	Favorable outcome in hypothermia group, no difference in mortality
TTM2, 2021[58]	1850	OHCA, any etiology, regardless of rhythm (excluded unwitnessed asystole)	33°C (91°F) for 24 hours versus 37°C (99°F)	No difference in functional neurologic outcome or mortality
CAPITAL CHILL, 2021[61]	389 (single center)	OHCA, any rhythm, any etiology	31°C (88°F) for 24 hours versus 34°C (93°F) versus for 24 hours	No difference in functional neurologic outcome or mortality

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TABLE 2-3 **Neuroprognostic Tests**[a]

Test	Good prognosis	Poor prognosis	Timing	Notes
Neurologic examination: Full Outline of UnResponsiveness (FOUR) score	Motor response localizing	Absent pupillary and corneal reflexes bilaterally for ≥72 hours; status myoclonus <48 hours with associated highly malignant EEG pattern	Daily; base prognostication 72 hours after arrest, off sedation	Poor motor examination no longer considered highly specific for poor prognosis
EEG	Early return of continuous, reactive, normal voltage background	Highly malignant pattern (suppressed or burst suppressed, with or without epileptiform discharges)	Continuous monitoring until awakening; or routine EEG at 12-24 hours and repeated after sedation weaning (48-72 hours) for patients still comatose	Highly malignant EEG patterns might evolve over time and follow a trend; reactivity should be assessed because its presence might portend to a better outcome
Somatosensory-evoked potentials	Amplitude of N20 potentials ≥2.5 μV	Bilaterally absent N20 responses 48 hours or later	Triage by EEG results; for patients still comatose at 48-72 hours	Bilateral, technically optimal assessment in patients without cortical responses is mandatory
Chemical biomarkers Neuron-specific enolase	Serum neuron-specific enolase ≤17 μg/L	High concentration at 48 hours or later; increasing serial concentrations	Daily for first 3 days; omit or interrupt if patient wakes up	Trend over 3 days (of neuron-specific enolase) might be helpful to exclude contamination; rising values over 24-48 hours suggest a brain origin
CT of the brain	Not applicable	Diffuse anoxic brain injury (reduced gray-white matter differentiation/ratio and sulcal effacement)	For patients still comatose at 48-72 hours	CT on admission helps exclude a central nervous system cause of cardiac arrest (eg, intracranial hemorrhage)
MRI of the brain	Not applicable	Diffuse and extensive anoxic injury	Day 3-5 after arrest	Necessary only if initial CT does not already show severe anoxic brain injury; advanced techniques (diffusion tensor imaging, functional MRI [fMRI]) might be considered in specialized centers

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requires proper technique, timing, and a detailed understanding of potential clinical confounders that might affect the results.

Clinicians must guide surrogates of unresponsive patients through shared decision making despite prognostic uncertainty. To do so, clinicians should outline potential best-case and worst-case outcomes, emphasizing that the full potential for recovery is evident only months after arrest, and elicit patient values and preferences.[94] In many cases, early decisions about lifesaving interventions (ie, mechanical circulatory support, emergent surgery, cardiac catheterization, dialysis) must be made before clinicians have the results of prognostic tests. The emphasis should be on maintaining prognostic humility in the first few days after arrest. Transfer to specialty centers with expertise in postarrest care and neuroprognostication may improve outcomes after arrest.[84,95]

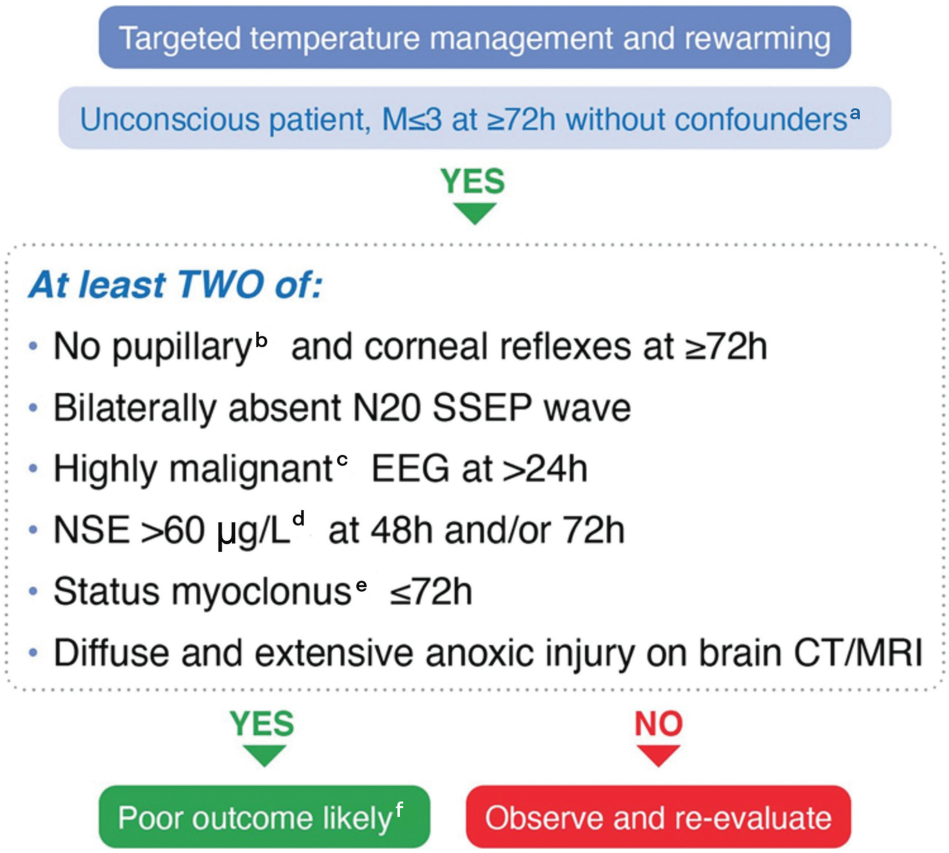
Targeted temperature management and rewarming
Unconscious patient, M≤3 at ≥72h without confounders[a]
YES
At least TWO of:
• No pupillary[b] and corneal reflexes at ≥72h
• Bilaterally absent N20 SSEP wave
• Highly malignant[c] EEG at >24h
• NSE >60 µg/L[d] at 48h and/or 72h
• Status myoclonus[e] ≤72h
• Diffuse and extensive anoxic injury on brain CT/MRI
YES
NO
Poor outcome likely[f]
Observe and re-evaluate

FIGURE 2-6

European Resuscitation Council prognostication guidelines after resuscitation from cardiac arrest.

NSE = neuron-specific enolase; SSEP = somatosensory evoked potential.

[a] Major confounders (M) may include sedation, neuromuscular blockade, hypothermia, severe hypotension, hypoglycemia, sepsis, and metabolic and respiratory derangements.

[b] Use an automated pupillometer, when available, to assess pupillary light reflex.

[c] Suppressed background with or without periodic discharges or burst suppression, according to the American Clinical Neurophysiology Society.

[d] Increasing NSE values between 24 and 48 hours or 24 and 48 hours and 72 hours further confirm a likely poor outcome.

[e] Defined as a continuous and generalized myoclonus persisting for 30 minutes or more.

[f] Caution in case of discordant signs indicating a potentially good outcome.

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KEY POINTS

- Cerebral edema can be caused or exacerbated by potentially preventable post–cardiac arrest insults (eg, hyperthermia or hyperosmolarity).
- Fever should be avoided after cardiac arrest because each degree above 37°C (99°F) is associated with worse outcomes, but some subsets of patients with hypoxic-ischemic brain injury may benefit from hypothermia.
- Continuous temperature monitoring is necessary after cardiac arrest.
- It is unclear whether aggressive suppression of rhythmic or periodic EEG patterns improves neurologic outcomes for patients who are comatose after cardiac arrest.
- EEG can help distinguish myoclonus subtypes, and patients with a continuous background after cardiac arrest have a better prognosis.
- A patient-centered strategy for the treatment and prevention of secondary brain injury is necessary for patients with hypoxic-ischemic brain injury.

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LONG-TERM OUTCOMES

Patients with hypoxic-ischemic brain injury have a wide range of long-term outcomes, ranging from functional independence to death. Outcomes of patients after arrest are commonly reported by using crude ordinal scales, such as the modified Rankin Scale (mRS) and Cerebral Performance Category, dichotomized as either a good or poor outcome.[96] Poor outcomes include patients who have died, are comatose, or are awake and functionally dependent (ie, mRS 4 to 6 or Cerebral Performance Category 3 to 5).[93,96]

Survival to hospital discharge ranges between 10% and 45% for patients after arrest and varies depending on local practices related to withdrawal of life-sustaining therapies.[93,96,97] Death from cardiovascular instability or multisystem organ failure is the main cause of death in the first 48 to 72 hours from a return of spontaneous circulation, but after that, two-thirds of deaths are the result of brain injury (FIGURE 2-7 and CASE 2-2).[81] In the United States, tens of thousands of patients annually have excellent recoveries.[98] The majority of patients who regain consciousness do so in the first 4 to 6 days, but awakening can be delayed up to 2 weeks,[99] usually in the setting of targeted temperature management or sedative use.[100] The most common cause of death for comatose patients with hypoxic-ischemic brain injury is withdrawal of life-sustaining therapies based on perceived poor neurologic prognosis.[27,101] Death by

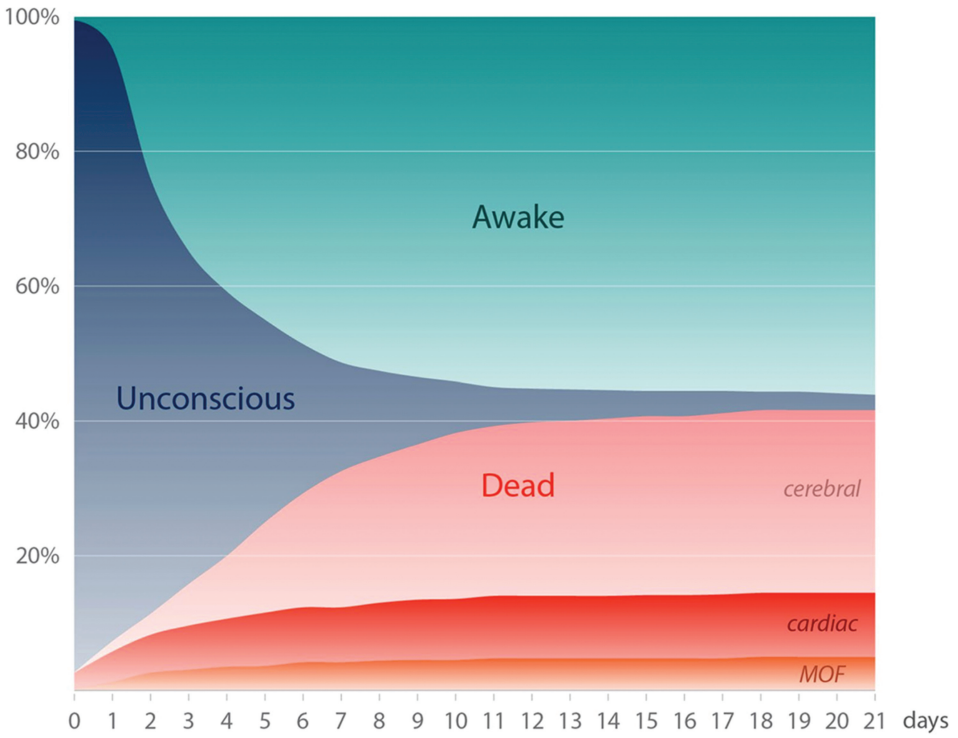

FIGURE 2-7

Time course of the outcome during the first 3 weeks after return of spontaneous circulation in 939 comatose patients included in the targeted temperature management trial. The stacked area chart shows the cumulative percentage of patients who regained consciousness or died. The causes of death are also displayed.

MOF = multiple organ failure.

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neurologic criteria accounts for 5% to 20% of all deaths for patients with hypoxic-ischemic brain injury (CASE 2-2).[102-104] Brain death is associated with cerebral edema on head CT, nonshockable initial rhythm, lower serum levels of sodium, and a neurologic cause of the arrest.[104,105]

Health disparities exist for post–cardiac arrest patient outcomes. Black and Latino patients have poorer outcomes compared with White patients and also receive lower rates of cardiopulmonary resuscitation and fewer postarrest interventions.[106] Gender differences in post–cardiac arrest outcomes also are present. Compared with men, women are less likely to survive to hospital discharge.[107] An ongoing area of research is elucidating the mechanisms that lead to these wide disparities in order to mitigate them.[106]

Patients who survive to hospital discharge can have a wide range of outcomes. At one site, 20% of hospitalized patients who survived to discharge had an mRS of 5. One year later, 40% of these patients died, and 20% still could not follow any commands. The proportion of patients who change their outcome over time varies across hospital sites throughout the world. The natural history of patients discharged from the hospital has not been well established. Current literature is limited by small sample sizes, single-center data, and infrequent long-term follow-up. The grading scales currently lack granular, patient-centered data. For patients who survive to hospital discharge with a good outcome, many have long-term issues with cognition, anxiety, depression, and posttraumatic stress disorder.[98,108,109] Understanding these patients' trajectory and long-term sequelae is to vital to creating postdischarge interventions (ie, rehabilitation) that further improve outcomes.

KEY POINTS

- **Neuroprognostication after hypoxic-ischemic brain injury should incorporate multimodal testing.**
- **The anticipated outcome for many patients after cardiac arrest is indeterminate, and the extent to which they will improve is evident only after 3 months.**
- **The emphasis should be on avoiding nihilism in the first few days after cardiac arrest.**
- **Following cardiac arrest, death from cardiovascular instability or multisystem organ failure is the main cause of death in the first 48 to 72 hours from a return of spontaneous circulation, but after that, two-thirds of deaths are the result of brain injury.**

CONCLUSION

Emergent management of hypoxic-ischemic brain injury requires intensive and individualized care. The focus is on the prevention and treatment of primary and secondary brain injury. Primary brain injury is minimized by excellent initial resuscitative efforts. Secondary brain injury prevention requires the detection and correction of many pathophysiologic processes that develop in the hours to days after arrest. Neurologists must use a multimodal approach to neuroprognostication while recognizing and acknowledging the shortcomings of each technique and the fact that prognosis after hypoxic-ischemic brain injury is often indeterminate until months after arrest.

ACKNOWLEDGEMENTS

The author thanks Jonathan Elmer for helping with the conceptualization of ideas and editing of the manuscript.

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